and then further computational processing may occur, which generates additional optimized sequences in the neighborhood of the global optimum.

## REMARKS

Claims 1, 3 and 10-18 are pending in the present application.

Applicants respectfully submit that Claims 10-18 are not drawn to a non-elected invention, but rather further limit the base claims (Claim 1). The claimed subject matter in each group is related by a "commonality of operation, function and effect" (see MPEP § 806.04(e)), election of a group is improper. Additionally, MPEP § 803 states that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions."

Applicants' claims do not provide independent and patentably distinct inventions. The claimed components are integrally related to each other in that the secondary library of secondary sequences is synthesized using various techniques. Thus, the claims operate as a common operation, function and effect.

Claims 10-12 provide for synthesizing a plurality of the secondary sequences generated by the method of Claim 1. Claim 13 is another embodiment of the claimed invention, where step b) uses a probability distribution of amino acid residues, instead of generating a list of primary variants positions of the primary library directly. Claim 14 uses the method of claim 13, but the variants generated from the primary library have at least one variant in the secondary library that was not in the primary library. Claim 15, provides for synthesizing a plurality of the secondary sequences from the method of Claim 13. Claims 16-18 are compositions generated from the secondary variant proteins. The claims merely demonstrate alternative embodiments of the claimed invention and further limit the scope of the claims. Therefore, Applicants respectfully request reconsideration and examination of Claims10-18.

**In the Specification:**

**- Embedded Hyperlinks**

All references to the hyperlinks and/or other forms of browser-executable code have been deleted from the Specification.

**- Incorporation by Reference:**

Applicants respectfully submit that referenced incorporated material is nonessential subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Therefore, incorporation by reference is proper. In light of the foregoing, the Applicants request reconsideration and withdrawal of the objection to the Specification.

**- Updated Patent Status**

Applicants respectfully submit the above-replacement paragraphs for page 2, lines 10-12; page 16, lines 17-31; page 18, lines 1-4; beginning on page 19, line 29, ending on page 20 at line 6; page 21 lines 9-21; beginning on page 21 at line 28, ending on page 22 line 12; page 24, lines 4-6, and page 27, lines 11-22 to update the status of a reference. USSN 09/127,926 issued as US Patent No. 6,269,312 on July 31, 2001. No new matter has been added by these amendments.

**Lack of Utility:**

Claims 1 and 3 are rejected under 35 U.S.C. §101. The Office Action asserts that no specific or well-established utility has been disclosed. Reconsideration under 37 CFR 1.111 is requested.

The methodology of the present invention provides a method for computationally screening variant protein sequence libraries to generate secondary libraries of useful variant protein sequences, which when synthesized find use in a wide variety of applications, ranging from industrial to pharmacological uses. Additionally, the methodology of the present invention allows for the rapid screening of large numbers of potential variant sequences for useful variants and the selection of proteins with useful properties. Greater diversity of protein sequences may be obtained by the method of the present invention. See Specification at page 2, lines 17-28; page 5, lines 13-24; page 6, lines 23-30; and page 7, lines 4-25.

The Applicants respectfully draw the Examiner's attention to the Utility Guidelines:
In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101. As the CCPA stated in In re Langer:

> "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."

Thus, Langer and subsequent cases direct the Patent Office to presume that a statement of utility made by an applicant is true. For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Patent Office personnel should not begin an inquiry by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate. Thus, Patent Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons.

Compliance with § 101 is a question of fact. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Patent Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. To do this, Patent Office personnel must provide evidence sufficient to show that a person of ordinary skill in the art would consider the statement of asserted utility "false". A person of ordinary skill must have the benefit of both facts and reasoning in order to assess the truth of a statement. This means that if the applicant has presented facts that support the reasoning used in asserting a utility, Patent Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility. (MPEP §2107.02IIIA). The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false). The Examiner has not met this burden.

Additionally, no further characterization of the present invention is necessary to demonstrate or confirm a "real world" use because the method of the present invention has been shown to work as claimed. See also U.S. Patent Nos. 6,188,965; 6,296,312; 6,403,312; PCT/US98/07254 and PCT/US01/40091.

Accordingly, the Applicants submit that the present invention has utility under §101. As further outlined in the Guidelines:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evid nce and reasoning provided). An assertion is credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the

> facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.

Thus, the burden is shifted to the Examiner. The Examiner analogizes a library to a composition of matter, which has to undergo screening to isolate and identify a product, citing Brenner v. Manson, 148 USPQ 689 (1966). Applicants respectfully disagree because the protein variants to be screened by the method of the present invention, synthesized and/or tested find utility in their respective fields. For example, for purposes of the present invention, it does not matter what the class of proteins are. The method of the claimed invention, screens for useful variants having desired protein characteristics. See for example, Specification at page 5, lines 15-18; page 5, lines 20-21; and page 38, lines 23-26. For example, the variants produced from the method of the present invention may find use as therapeutic proteins. See Specification beginning at page 38, line 27, ending on page 39, line 2.

In conclusion, as outlined above, the present invention has utility under §101 and Applicants respectfully request that the rejection be withdrawn.

**Claim Rejection 35 USC §112, first paragraph**

Claims 1 and 3 are rejected under 35 USC §112, first paragraph because the specification while enabling for the enzymes protein design using specific program design, does not reasonably provide enablement for any type of secondary library of scaffold protein variants or sequences.

The Applicants respectfully disagree for the following reasons. §112 does not require such extensive disclosure. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ81, 94 (Fed.Cir. 1986), cert.denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ481, 489 (Fed. Cir. 1984).

Furthermore, "[a]ll that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. Se, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." (See MPEP §2164.08)

The Applicant respectfully draws the Examiner's attention to page 8, lines16-19; and page 9, lines 13-20 of the Specification as filed, where there is a discussion of secondary library of scaffold protein or variant sequences.

The enablement requirement refers to the requirement of 35 USC 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent.

With respect to the scope of the enabling disclosure not commensurate with the scope provided in the Specification, there is disclosure of using a computational design program, and preferably PDA™ technology as embodiments of the invention. See Specification at page 2, lines 10-13; page 8, lines 4-8; and page 16, lines 17-31.

Applicants respectfully point to *In re Goffe*, 191 USPQ429 (CCPA 1976), where the court stated:

> "For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional propose of promoting progress in the useful arts."

Additionally, in *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976), the court further stated:

> "Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed."

Therefore, in conclusion, Applicants submit that the Specification taken in conjunction with the state of the art at the time the invention was filed fully enables a person skilled in the art to practice the method of the invention without undue experimentation. Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejection under 35 USC §112, second paragraph**

Claims 1 and 3 are rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter, which the applicant regards as the invention.

Claims 1 is rejected as being unclear as to the method by which a list of primary variant positions in the primary library is generated. "The recited "filtered set of scaffold protein primary variants" is indefinite within the claimed context. The term does not correspond with the specification at page 2, line 19. The specification recites a rank-ordered list of scaffold protein primary variant sequences and not a filtered set of scaffold protein primary variant sequences." Furthermore, the Office Action states that the terms: "primary;" "secondary;" "set;" and "plurality" are indefinite.

Applicants respectfully submit that the term "rank-ordered list" is an optional embodiment of the claimed invention. See Specification at page 11, line 25-27. With respect to the term "filtered set," Applicants respectfully draw the Examiner's attention to the Specification beginning on page 26, line 20, ending on page 27, line 4. "Filtered set" as used in the present application is the optimized protein sequences that are generated using some sort of ranking or scoring function. (See page 26, lines 27-28). Applicants respectfully submit the definition of the rejected term is definite as disclosed and request reconsideration and withdrawal of the claim rejection.

The term "primary" has a variety of contexts. With respect to a "primary library" it is defined in the Specification on page 11, lines 3-7. The term "secondary" as used in the present invention is read in light of the specification and in the context of its use. Additionally, the recitation of "primary" and "secondary" as used in the specification and claims is not arbitrary as the Office Action suggests, but rather describes their parts in the claimed process, thus primary and secondary as used herein have their ordinary meanings. The term "set," as used herein has its ordinary meaning in the context of the use. With respect to the term "plurality" as used herein means more than one. Applicants respectfully submit that only a "reasonable" degree of particularity and distinctness is required. MPEP 2173.02.

With regard to the metes and bounds of the sequences generated by the method of the present invention, there is no criticality of the size or number of residues used because they depend upon the protein, characteristics desired and size of the library desired by the user. There is no requirement for a minimum or maximum number or size. When read in light of the specification, one skilled in the art would understand what was being made when talking about a primary or secondary library.

As stated in the MPEP §2173.05(a):

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). See also MPEP § 2111 - § 2111.01. When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

In reviewing a claim for compliance with 35 U.S.C. §112, the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required (See MPEP §2173.02). If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the statute demands no more.

In light of the foregoing arguments, Applicants respectfully request the reconsideration and withdrawal of the rejection of Claims 1 and 3.

**Claim Rejections – 35 USC §102**

Claims 1 and 3 have been rejected under §102(b) as being anticipated by Dahiyat et al. (Protein Science). The Office Action asserts that "Dahiyat discloses at page 1333-4, discloses a method using a protein design algorithm for the solvent exposed residues of homodimeric GCN4-pl. The Office Action concludes that "the specific process steps of Dahiyat fully meet the broad claimed method." Applicant's respectfully disagree because the cited reference neither suggests or teaches the generation of libraries per se, and does not teach the generation of secondary libraries.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)."

Furth rmore, the present invention may be distinguished from the cited references because there is no suggestion or teaching of generating a secondary library from secondary sequences, differing from the primary sequence(s). Therefore, the claims of the present invention are not anticipated by the cited reference because each and every element as set forth in the claim is not found, either expressly or inherently described, in a single prior art reference. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the claim rejections.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."** Please direct any calls in connection with this application to the undersigned at (626) 737-8019.

Dated: May 19, 2003

Respectfully submitted,

By: _____

Joyce L. Morrison, Reg. No. 31,902

Xencor
111 W. Lemon Avenue
Monrovia, California 91016
Telephone: (626) 737-8019
Fax No. (626) 256-3562

## VERSION TO SHOW CHANGES MADE TO THE SPECIFICATION

Page 13, lines 9-16

The source of the sequences can vary widely, and include taking sequences from one or more of the known databases, including, but not limited to, SCOP (Hubbard, et al., Nucleic Acids Res 27(1):254-256. (1999)); PFAM (Bateman, et al., Nucleic Acids Res 27(1):260-262. (1999)); VAST (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); CATH (Orengo, et al., Structure 5(8):1093-1108. (1997)); PhD Predictor ~~(http://www.embl-heidelberg.de/predictprotein/predictprotein.html)~~ (Rost B, Sander C, Schneider R., PHD--an automatic mail server for protein secondary structure prediction. Comput Appl Biosci. 1994 Feb;10(1):53-60); Prosite (Hofmann, et al., Nucleic Acids Res 27(1):215-219. (1999)); PIR ~~(http://www.mips.biochem.mpg.de/proj/protseqdb/)~~ (Wu CH, Yeh LS, Huang H, Arminski L, Castro-Alvear J, Chen Y, Hu Z, Kourtesis P, Ledley RS, Suzek BE, Vinayaka CR, Zhang J, Barker WC. The Protein Information Resource. Nucleic Acids Res. 2003 Jan 1;31(1):345-7.); GenBank ~~(http://www.ncbi.nlm.nih.gov/)~~ (ncbi.nlm.nih.gov); PDB ~~(www.resb.org)~~ PDB (H. M. Berman, T. Battistuz, T. N. Bhat, W. F. Bluhm, P. E. Bourne, K. Burkhardt, Z. Feng, G. L. Gilliland, L. Iype, S. Jain, P. Fagan, J. Marvin, D. Padilla, V. Ravichandran, B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook and C. Zardecki, The Protein Data Bank, Acta Cryst. (2002). D58, 899-907) and BIND (Bader, et al., Nucleic Acids Res 29(1):242-245. (2001)).

Page 14, lines 14-21

Similarly, structural alignment of structurally related proteins can be done to generate sequence alignments. There are a wide variety of such structural alignment programs known. See for example VAST from the NCBI ~~(http://www.ncbi.nlm.nih.gov:80/Structure/VAST/vast.shtml)~~ NCBI (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); SSAP (Orengo and Taylor, Methods Enzymol 266(617-635 (1996)) SARF2 (Alexandrov, Protein Eng 9(9):727-732. (1996)) CE (Shindyalov and Bourne, Protein Eng 11(9):739-747. (1998)); (Orengo et al., Structure 5(8):1093-108 (1997); Dali (Holm et al., Nucleic Acid Res. 26(1):316-9 (1998), all of which are incorporated by reference). These structurally-generated sequence alignments can then be examined to determine the observed sequence variations.

Page 14, lines 22-32

Primary libraries can be generated by predicting secondary structure from sequence, and then selecting sequences that are compatible with the predicted secondary structure. There are a number of secondary structure prediction methods, including, but not limited to, threading (Bryant and Altschul, Curr Opin Struct Biol 5(2):236-244. (1995)), Profile 3D (Bowie, et al., Methods Enzymol 266(598-616 (1996); MONSSTER (Skolnick, et al., J Mol Biol 265(2):217-241. (1997); Rosetta (Simons, et al., Proteins 37(S3):171-176 (1999); PSI-BLAST (Altschul and Koonin, Trends Biochem Sci 23(11):444-447. (1998)); Impala (Schaffer, et al., Bioinformatics 15(12):1000-1011. (1999)); HMMER (McClure, et al., Proc Int Conf Intell Syst Mol Biol 4(155-164 (1996)); Clustal W ~~(http://www.ebi.ac.uk/clustalw/)~~ Higgins D., Thompson J., Gibson T.Thompson J.D., Higgins D.G., Gibson T.J.(1994).CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting,position-specific gap penalties and weight matrix choice.Nucleic Acids Res. 22:4673-4680; BLAST (Altschul, et al., J Mol Biol 215(3):403-410. (1990)), helix-coil transition theory (Munoz and Serrano, Biopolymers 41:495, 1997), neural networks, local structure alignment and others (e.g., see in Selbig et al., Bioinformatics 15:1039, 1999).

Page 2, lines 10-12

In particular, U.S.S.N.s 60/061,097, 60/043,464, 60/054,678, 09/127,926, now US Patent No. 6,269,312 and PCT US98/07254 describe a method termed "Protein Design Automation", or PDA, that utilizes a number of scoring functions to evaluate sequence stability.

Page 16, lines 17-31

In a preferred embodiment, the computational method used to generate the primary library is Protein Design Automation (PDA), as is described in U.S.S.N.s 60/061,097, 60/043,464, 60/054,678, 09/127,926, now US Patent No. 6,269,312, and PCT US98/07254, all of which are expressly incorporated herein by reference. Briefly, PDA can be described as follows. A known protein structure is used as the starting point. The residues to be optimized are then identified, which may be the entire sequence or subset(s) thereof. The side chains of any positions to be varied are then removed. The resulting structure consisting of the protein backbone and the remaining sidechains is called the template. Each variable residue position is then preferably classified as a core residue, a surface residue, or a boundary residue; each classification defines a subset of possible amino acid residues for the position (for example, core residues generally will be selected from th set of hydrophobic residues, surface residues generally will be

selected from the hydrophilic residues, and boundary residues may be either). Each amino acid can be represented by a discrete set of all allowed conformers of each side chain, called rotamers. Thus, to arrive at an optimal sequence for a backbone, all possible sequences of rotamers must be screened, where each backbone position can be occupied either by each amino acid in all its possible rotameric states, or a subset of amino acids, and thus a subset of rotamers.

Page 18, lines 1-4

As outlined in U.S.S.N. 09/127,926, now US Patent No. 6,269,312, the protein backbone (comprising (for a naturally occurring protein) the nitrogen, the carbonyl carbon, the $\alpha$-carbon, and the carbonyl oxygen, along with the direction of the vector from the $\alpha$-carbon to the $\beta$-carbon) may be altered prior to the computational analysis, by varying a set of parameters called supersecondary structure parameters.

Page 19, beginning on line 29, ending on page 20 at line 6

The classification of residue positions as core, surface or boundary may be done in several ways, as will be appreciated by those in the art. In a preferred embodiment, the classification is done via a visual scan of the original protein backbone structure, including the side chains, and assigning a classification based on a subjective evaluation of one skilled in the art of protein modeling. Alternatively, a preferred embodiment utilizes an assessment of the orientation of the C$\alpha$-C$\beta$ vectors relative to a solvent accessible surface computed using only the template C$\alpha$ atoms, as outlined in U.S.S.N.s 60/061,097, 60/043,464, 60/054,678, 09/127,926, now US Patent No. 6,269,312, and PCT US98/07254. Alternatively, a surface area calculation can be done.

Page 21, lines 9-21

Once the group of potential rotamers is assigned for each variable residue position, processing proceeds as outlined in U.S.S.N. 09/127,926, now US Patent No. 6,269,312, and PCT US98/07254. This processing step entails analyzing interactions of the rotamers with each other and with the protein backbone to generate optimized protein sequences. Simplistically, the processing initially comprises the use of a number of scoring functions to calculate energies of interactions of the rotamers, either to the backbone itself or other rotamers. Preferred PDA

scoring functions include, but are not limited to, a Van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, a secondary structure propensity scoring function and an electrostatic scoring function. As is further described below, at least one scoring function is used to score each position, although the scoring functions may differ depending on the position classification or other considerations, like favorable interaction with an $\alpha$-helix dipole. As outlined below, the total energy which is used in the calculations is the sum of the energy of each scoring function used at a particular position, as is generally shown in Equation 1:

*Page 21 beginning at line 28, ending on page 22, line 12*

As outlined in U.S.S.N.s 60/061,097, 60/043,464, 60/054,678, 09/127,926, now US Patent No. 6,269,312, and PCT US98/07254, any combination of these scoring functions, either alone or in combination, may be used. Once the scoring functions to be used are identified for each variable position, the preferred first step in the computational analysis comprises the determination of the interaction of each possible rotamer with all or part of the remainder of the protein. That is, the energy of interaction, as measured by one or more of the scoring functions, of each possible rotamer at each variable residue position with either the backbone or other rotamers, is calculated. In a preferred embodiment, the interaction of each rotamer with the entire remainder of the protein, i.e. both the entire template and all other rotamers, is done. However, as outlined above, it is possible to only model a portion of a protein, for example a domain of a larger protein, and thus in some cases, not all of the protein need be considered. The term "portion", as used herein, with regard to a protein refers to a fragment of that protein. This fragment may range in size from 10 amino acid residues to the entire amino acid sequence minus one amino acid. Accordingly, the term "portion", as used herein, with regard to a nucleic refers to a fragment of that nucleic acid. This fragment may range in size from 10 nucleotides to the entire nucleic acid sequence minus one nucleotide.

Page 24, lines 4-6

Once the singles and doubles energies are calculated and stored, the next step of the computational processing may occur. As outlined in U.S.S.N. 09/127,926, now US Patent No. 6,269,312, and PCT US98/07254, preferred embodiments utilize a Dead End Elimination (DEE) step, and preferably a Monte Carlo step.

Page 27, lines 11-22

In a preferred embodiment when scoring is used, although this is not required, the primary library comprises the globally optimal sequence in its optimal conformation, i.e. the optimum rotamer at each variable position. That is, computational processing is run until the simulation program converges on a single sequence which is the global optimum. In a preferred embodiment, the primary library comprises at least two optimized protein sequences. Thus for example, the computational processing step may eliminate a number of disfavored combinations but be stopped prior to convergence, providing a library of sequences of which the global optimum is one. In addition, further computational analysis, for example using a different method, may be run on the library, to further eliminate sequences or rank them differently. Alternatively, as is more fully described in U.S.S.N.s 60/061,097, 60/043,464, 60/054,678, 09/127,926, now US Patent No. 6,269,312, and PCT US98/07254, the global optimum may be reached, and then further computational processing may occur, which generates additional optimized sequences in the neighborhood of the global optimum.

USSN: 09/927,790
Filing Date: August 10, 2001

## APPENDIX OF PENDING CLAIMS

1. A method for generating a secondary library of scaffold protein variants comprising:

a) providing a primary library comprising a filtered set of scaffold protein primary variant sequences;

b) generating a list of primary variant positions in said primary library;

c) combining a plurality of said primary variant positions to generate a secondary library of secondary sequences.

3. A method according to claim 1 further comprising synthesizing a plurality of said secondary sequences.

10. A method according to claim 3 wherein said synthesizing is done by multiple PCR with pooled oligonucleotides.

11. A method according to claim 10 wherein said pooled oligonucleotides are added in equimolar amounts.

12. A method according to claim 10 wherein said pooled oligonucleotides are added in amounts that correspond to the frequency of the mutation.

13. A method according to Claim 1, wherein said generating step b) comprises a probability distribution of amino acid residues in a plurality of variant positions.

14. A method according to claim 13 wherein at least one of said secondary variants is different from said primary variant sequences.

15. A method according to claims 1 or 13 further comprising synthesizing a plurality of said secondary sequences.

16. A composition comprising a plurality of secondary variant proteins comprising a subset of said secondary library according to claims 1, 10-13.

17. A composition comprising a plurality of secondary variant proteins comprising a subset of said secondary library according to claim 14.

18. A composition comprising a plurality of secondary variant proteins comprising a subset of said secondary library according to claim 15.